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First Named Inventor: Michael T Milbocker

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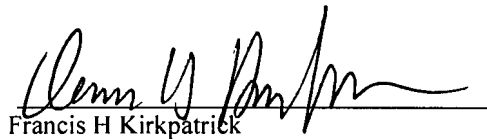
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**DECLARATION UNDER RULE 132**

I, Michael T. Milbocker, Ph.D., declare as follows:

1. I am the inventor in the above referenced patent application.
2. During the development of the prepolymer used as an adhesive in the application having serial no. 10/020,331, formulations were synthesized of greater and lesser proportions of propylene oxide (PO) subunits than the 10% to 30% range currently claimed.
3. As a limiting case of high PO content, pure diol-terminated block polymers of propylene oxide (PO) and of ethylene oxide (EO) were mixed in equal proportion (50:50) by weight. Toluene diisocyanate (TDI) was added to chain extend the mixture to

approximately 1000 D molecular weight and the mixture subsequently was trimerized with trimethylolpropane (TMP). The OH groups on the ends of the chain extended diols were already functionalized with TDI and readily reacted with the TMP to form trimers. Thus, the content of PO in the final block copolymer material as a function of alkylene oxide monomers is 50%.

This composition when applied to fresh bovine tissue was resistant to wetting the tissue surface. The composition polymerized without making bonds to the tissue, and once fully polymerized could easily be washed from the tissue surface with minimal force.

The composition when mixed with equal parts water formed two fractions: a polymerized foam fraction which precipitated from solution and an excluded water fraction. When the foam was removed from the excluded water fraction, it was found to be dry but flexible. This experiment shows that the material with 50% PO subunits did not form a hydrogel of 50% water, since most of the water remained separate from and was not taken by the polymerized block copolymer.

Thus, a content of 50% PO of alkylene oxide in the composition is too high to form a hydrogel forming material, and is not capable of being a hydrogel forming tissue adhesive. Muller's PO contents of 70% and higher are above this range and likewise will not produce a hydrogel forming material, or a tissue adhesive, after polymerization.

4. In later experiments, a 25:75 PO:EO ratio block copolymer polyol material, available commercially as "Voranol CP 1421", was used. The Voranol conveniently already is trimeric, and so does not require the added step of trimerization. The Voranol was mixed with a small excess of TDI (toluene diisocyanate), forming a block copolymer polyol tipped with isocyanate.

This composition, when mixed with equal parts of water, polymerized without separation to form a homogenous gel containing 50% water (as described in paragraph 47 of applicant's published application). The gel was wet to the touch, and significant water could not be expressed from the gel by the application of mechanical pressure (by hand). This is characteristic of a hydrogel. The ability to take up water and thus wet tissue is believed to be a reason for increased bond strength.

5. I therefore concluded, before the submission of the application in 2001, that an upper and lower range of PO content for synthesizing an effective tissue adhesive existed, and demonstrated that an effective tissue adhesive, having a removal force of above 4.5 lb per square inch, could be obtained from a block copolymer alkylene oxide polyol tipped with an isocyanate, provided that no more than about 30% of the monomers of the block copolymer polyol were polypropylene oxide.

It was believed that an ability to take up water and thus wet and bond to tissue was associated with the formation of a hydrogel. The upper limit on the PO content in polymerizable compositions containing EO/PO polyols capable of forming a hydrogel was believed to be approximately 30% PO.

6. The above experiments and conclusions support the description of the material found in paragraphs [0045] – [0048] of the present application as published, which state:

[0045] The present invention relates to a 1-part surgical adhesive wherein covalent bonds are formed with body tissue and a hydrogel is formed of body fluids. However, the vast majority of NCO-terminated hydrophilic urethane prepolymers do not form such hydrogels. Urethane prepolymers are deemed hydrophilic if they incorporate in the urethane structure between 2 and 10% water. Such prepolymers are not effective as surgical adhesives since they are not hydrophilic enough and do not form hydrogels. Such prepolymers, when placed in an environment where the water exceeds 10% of the prepolymer volume polymerize internally without linking to tissue or fail to form a solid.

[0046] Consequently, the majority of hydrophilic polyether polyols can be excluded for use in the present invention. In particular, the polyol of choice is a tri-functional form of PE/PO block polymer. The ratio of PE to PO is critical to the formation of the hydrogel. The PE provides the necessary hydrophilic nature, and the PO provides hydrogel strength. For

example, adhesives formed from pure PE tend to breakdown in the body and swell to 2 to 10 times their original volume within several hours.

[0047] Adhesives of highest reliability will be non-absorbable and contain 10 to 30% PO. Adhesives with greater than 30% PO will not form hydrogels comprising greater than 50% water by volume.

[0048] In certain medical applications an absorbable adhesive is desirable. The rate of absorption can be controlled by adjusting the amount of PO, typically about 10% for adhesives with a residence time of about 1-2 weeks.

7. In addition, it also is important to have some free isocyanate in the composition to promote adhesion to tissue. At the same time, it is important to maintain the free isocyanate content of the composition to be not only at least 1% (for tissue adhesion), but also less than 5% (for safety reasons). Muller, on the other hand, takes the opposite approach, always including much higher amounts of free or excess isocyanate.

Thus, Muller et. al., differs significantly from applicant's claims in the amount of "free" low molecular weight isocyanate in the preparation. Muller always uses a large excess of low MW isocyanate (at least 10%, generally at least about 25%) in the mixture, in order to provide a rapid creation of foam upon reaction with a relatively small amount of water. The large excess of low MW isocyanate in combination with water creates a blowing agent intended to substitute for halocarbon blowing agents.

In Muller's preferred reaction system, beginning at col 7 line 64, A is an isocyanate terminated prepolymer with an NCO (isocyanate) content of 2 to 15% by weight; B is a diphenylmethane diisocyanate compound having at least 20% NCO (isocyanate) by weight; plus a component C containing water and (8/14-15) comprising 1 to 5% of the weight; wherein A + B together contain 20 to 40% polyphenylisocyanates or residues thereof, and 80% to 60% of residues of isocyanate-reactive species.

In other words, the composition originally contained 20% to 40% by weight of an isocyanate such as methylene diisocyanate.

In Col 9 – 10 of Muller, MDI based polyisocyanates A through G are defined. B, C and G are various low molecular weight isocyanate mixtures. A, D, E and F are isocyanate tipped polymeric polyols with leftover isocyanate. The starting ratio of polyol to isocyanate is 750:250 (A); 752:321 (D), 27.3: 74.3 (E), and 26.8:73.2 (F), which in each case is about 25% isocyanate – by weight – and 75% polyol.

Every one of the polymer-containing preparations has an excess of free isocyanate. In use, they are mixed with more low molecular weight isocyanate:

In Example 1, 80 parts of polymer (A), containing 25% isocyanate, is mixed with 10 parts each of isocyanates B and C, and then the mixture is to be polymerized.

In Example 2, 90 parts of polymer (A), containing 25% isocyanate, is mixed with 10 parts isocyanate B.

In Example 3, 90 parts of polymer (D), containing 25% isocyanate, is mixed with 10 parts isocyanate C.

In Example 4, 90 parts of polymer (E) containing 25% isocyanate, is mixed with 10 parts “Suprasec” (isocyanate C; col 9 line 54).

In Example 5, 90 parts of polymer (F) containing 25% isocyanate, is mixed with 10 parts Suprasec. (isocyanate C; col 9 line 54).

In Example 6, 90 parts of polymer (A) containing 25% isocyanate, is mixed with 10 parts isocyanate G.

Thus, in every one of these examples of Muller, the percentage of free isocyanate is well over 10%, and probably is over 30%: 90 parts polymer, containing 25% free isocyanate, and 10% additional free isocyanate.

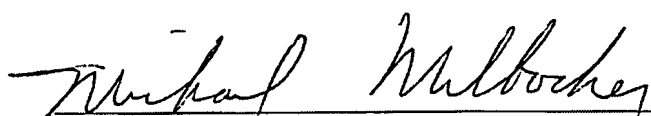
Example 7 of Muller et al. describes the process of conversion of the materials of Example 1 into a foam. Using a “mixing head” to sequentially mix ingredients together in a continuous stream, the isocyanates and polymers are blended 2.5 cm into the mixing head. Then, at the 13 cm level (col 12 line 37), the catalysts are added; then, at the 15 cm level, water is added (line 42), and at the 50 cm point (line 49), the creaming mixture is ejected (line 49 – 52).

Thus, in Muller the mixture before adding water clearly has a concentration of isocyanates not bonded to polyols of greater than 10%, and probably greater than 30%,

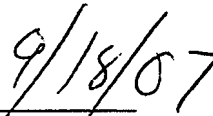
since the ratio of isocyanate to polyol, in the polymer mixtures A, D, E, and F, is 25%:75% - 25 g. isocyanate to 75 g. polyol, or 25% of the solution being free isocyanate (or low MW polymers of the isocyanate with itself), and these are then mixed with at least 10% by weight of pure free isocyanate. This is much higher than applicant's claimed composition which contains less than 5% free isocyanate.

8. In the six years of experimentation that have followed the initial patent application filing, I continue to find that having a minimum proportion of PO units in a tissue adhesive in a block copolymer polyol is necessary to minimize swelling and retain strength in the bond. I also continue to find that there is an upper limit of PO concentration in the block copolymer polyol, somewhat variable depending on the ratio of isocyanate residues to total polyol, but approximately 30% by number, above which the adhesive does not adhere well to tissue and does not form a hydrogel. Based on my experience, Muller's very high PO content of 70% or more in block copolymers will not provide a hydrogel-forming polymer of any sort, much less one that forms a hydrogel of 50% water or more. The experiment described above in paragraph 3 utilizing 50:50 PO:EO did not form a suitable hydrogel forming composition, from which I conclude that the even higher PO contents of Muller will not form a hydrogel and will not be suitable as a hydrogel forming adhesive.

9. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under 18 USC 1001, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.



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date

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